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Goh, Shermin S
Champagne, Pier Alexandre
Guduguntla, Sureshbabu
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Stereospecific Ring Contraction of Bromocycloheptenes through Dyotropic Rearrangements via Nonclassical Carbocation−Anion Pairs

Shermin S. Goh,[†,∥,#] Pier Alexandre Champagne,[‡,#] Sureshbabu Guduguntla,[†] Takashi Kikuchi,[§,⊥] Makoto Fujita,[§] K. N. Houk,*[,‡] and Ben L. Feringa*[,†]

[†]Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

[‡]Department of Chemistry and Biochemistry, University of California—Los Angeles, 607 Charles E. Young Drive East, Box 951569, Los Angeles, California 90095-1569, United States

[§]Department of Applied Chemistry, University of Tokyo, 7-3-1 Hongo, Bukyo-ku, Tokyo 113-8656, Japan

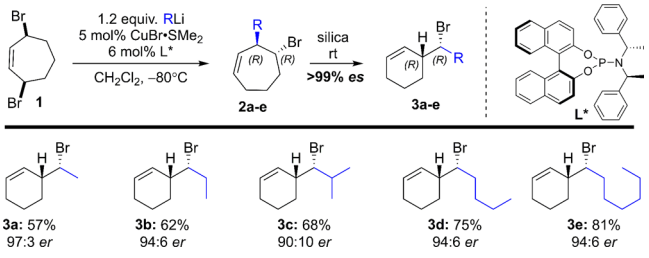
[⊥]Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8628, Japan

Supporting Information

ABSTRACT: Experimental and theoretical evidence is reported for a rare type I dyotropic rearrangement involving a [1,2]-alkene shift, leading to the regio- and stereospecific ring contraction of bromocycloheptenes. This reaction occurs under mild conditions, with or without a Lewis acid catalyst. DFT calculations show that the reaction proceeds through a nonclassical carbocation−anion pair, which is crucial for the low activation barrier and enantiospecificity. The *chiral* cyclopropylcarbinyl cation may be a transition state or an intermediate, depending on the reaction conditions.

In the course of our investigation of the desymmetrization of *meso*-3,7-dibromocycloheptene **1**, we discovered that the initially formed enantiomerically enriched homoallylic bromides **2** were spontaneously isomerized with retention of configuration to form chiral substituted cyclohexenes **3** (Scheme 1).[1] This reaction could be accelerated by Lewis acids such as silica or $ZnBr_2$, with no change in stereoselectivity. We have studied this reaction by a combination of experiments and computations, and now report that this involves a rare dyotropic rearrangement involving nonclassical cyclopropylcarbinyl cations on the reaction paths as either transition states or intermediates, depending on the conditions.

Scheme 1. Desymmetrization of 1 by AAS and Subsequent Rearrangement of Cycloheptenes 2 to Cyclohexenes 3[a,b]



[a]Isolated yields over two steps. [b]*er*'s of **2a−e** and **3a−e** were determined by chiral GC to be the same, so *es* is >99%.

The copper-catalyzed desymmetrization of **1** by asymmetric allylic substitution[2] (AAS) with organolithium reagents[3] initially afforded the expected products **2a−e** (>99:1 *dr*), as observed by NMR spectroscopy of the crude reaction mixtures [see Supporting Information (SI)]. The reaction also proceeded with high enantioselectivity, as determined by chiral GC.[1] However, upon exposure to silica, the bromocycloheptenes **2a−e** isomerized to afford six-membered cyclic homoallylic bromides **3a−e**. The ring contraction reaction proceeded with complete regioselectivity and enantiospecificity, as determined by chiral GC [see SI, part 1 and SI, part 2].

In fact, the rearrangement reaction was so facile that the transformation from cycloheptenes **2a−e** to cyclohexenes **3a−e** occurred even on neutral alumina, or when left standing in chloroform-*d* ($t_{1/2} \approx 6$ days). The major enantiomer of **3d**,[4] obtained as a colorless oil, was determined to be (*R*,*R*) by X-ray crystallography using only 5 μg of compound and the crystalline sponge method developed by the Fujita group[5] (Figure 1). A similar attempt was made to study the absolute configuration of its precursor **2d**; however, the rearrangement occurred while soaking in crystalline sponge, and only **3d** was detected when the X-ray analysis was performed.

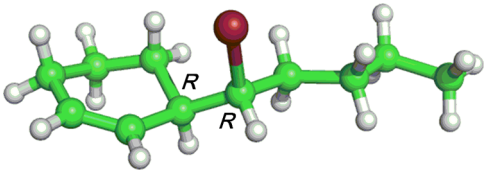


Figure 1. Ball-and-stick representation of the X-ray structure of **3d** determined by the crystalline sponge method.

The ring contraction reaction from **2a−e** to **3a−e**, interconverting the two isomeric homoallylic bromides, involves the 1,2-positional exchange of the alkenyl and bromo groups; thus it is formally a [2,2]-dyotropic rearrangement. These were first described in 1972 by M. T. Reetz as a class of pericyclic valence isomerizations involving the simultaneous

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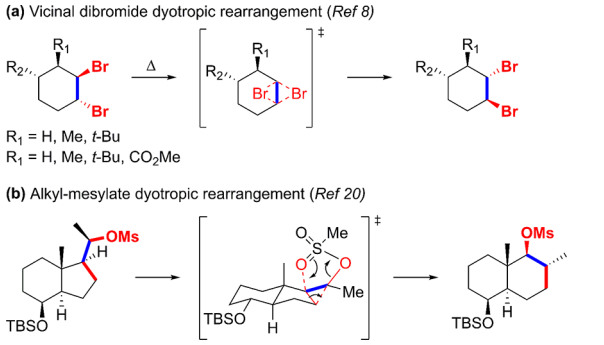
intramolecular migration of two σ-bonds.[6,7] Type I dyotropic rearrangements occur when the two migrating groups exchange their positions (e.g., the classic rearrangement of *anti* vicinal dibromides, Scheme 2a),[8] while in type II rearrangements the groups migrate to entirely different positions. Dyotropic reactions have become more common recently in organic and organometallic chemistry[9] and have even been applied to total syntheses.[9,10] The concerted migration of carbon chains through a [2,2]-shift on a static C−C scaffold is uncommon. $[_\sigma 2_s + {}_\sigma 2_s]$ processes are thermally forbidden by the Woodward−Hoffmann rules,[11,12] but the reaction becomes allowed if one migrating group has a lone pair and migrates with inversion. Nevertheless, such reactions are still rare because the activation barriers are usually quite high.[13]

Scheme 2. Uncatalyzed Concerted Type I Dyotropic Rearrangements Occurring on a Static C−C Scaffold



Until recently, the only experimental examples of such reactions involved highly strained lactones reacting under strenuous conditions. Examples of alkyl group migration are the ring expansion of β-lactones to butyrolactones promoted by stoichiometric magnesium bromide,[14−16] or the rearrangement of cage δ-lactones to γ-lactones at 350 °C on a quartz column.[17] Acyl group migration involving a β-lactone ring expansion promoted by stoichiometric Lewis acid is also known.[18] In recent years, milder dyotropic rearrangements have been discovered. Gutta and Tantillo proposed a 1,2-positional exchange of an alkyl group and a hydrogen atom in their computed biosynthetic pathway for formation of pentalenene in 2006.[19] More recently, Faza, Lopez, and co-workers reported the type I dyotropic ring expansion of hydrindane to decalin occurring at −78 °C upon mesylation (Scheme 2b).[20] To the best of our knowledge, a concerted and uncatalyzed type I dyotropic migration of a C−C π system is still unknown.

The mechanism of this rearrangement was investigated by NMR spectroscopy. Time-dependent aliquot studies with silica as reagent (500% w/w) for the rearrangement of bromocycloheptene **2d** showed that bromocyclohexene **3d** (>99% *es*) was the only product generated. This was observed in both polar aprotic (chloroform-*d*) and apolar (benzene-d_6) solvents, although the rate of reaction was slower in benzene-d_6 (Figure 2b,c); the lack of solvent dependence for selectivity indicates that the reaction does not proceed through a discrete carbocation. The use of Lewis acids (e.g., $ZnBr_2$ and TMSOTf) led to poorer selectivity in the rearrangement reaction, with ca. 5−10% of a different diastereoisomer **4d** observed (Figure 2d,e);[21] its formation may be explained by the ionization of product **3d** by the stronger Lewis acids [see SI]. There was, fortunately, no erosion in *ee* of the expected product. These reactions with Lewis acids could be monitored *in situ* by NMR time course experiments in either chloroform-*d* (Figure 2a) or benzene-d_6 with no difference in product ratio or enantiospecificity, although the reaction was always slower in the apolar solvent [see SI]. The reaction could also be performed with Brønsted acids [see SI], or with catalytic amounts of Lewis acids (Figure 2e), albeit at a much reduced rate. When conducted in the presence of radical scavenger BHT (1.0 equiv), the reaction profile did not change [see SI], indicating that a radical pathway was not involved.

To further understand the mechanism and specificity of the rearrangement, we performed DFT calculations on compound

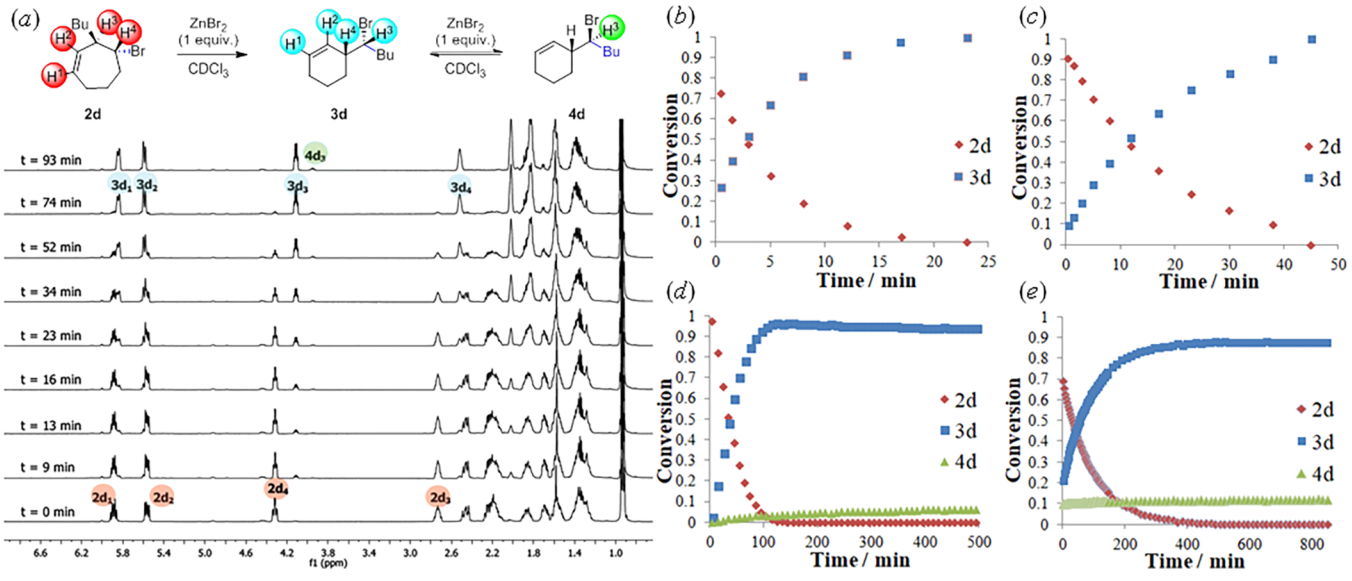


Figure 2. Left: (a) ^{1}H NMR spectroscopic profiles of bromocycloheptene **2d** with $ZnBr_2$ (1 equiv) in chloroform-*d* with increasing time; reaction scheme is shown at top. Right: Reaction progress of **2d** with silica (500% w/w) monitored by timed aliquots in (b) chloroform-*d* and (c) benzene-d_6. Reaction progress of **2d** monitored by *in situ* NMR spectroscopy with (d) $ZnBr_2$ (1 equiv) in chloroform-*d* and (e) TMSOTf (0.5 equiv) in chloroform-*d*.

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2a at the M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) level of theory,[22] using Gaussian 09.[23] The SMD solvation model[24] for $CHCl_3$ was used throughout. Computed structures were visualized using CYLview.[25] We first investigated whether a concerted uncatalyzed dyotropic rearrangement is plausible. The cycloheptene ring of **2a** has two low-energy conformations, where the methyl and bromo substituents are either pseudoaxial (**2a-ax**) or pseudoequatorial (**2a-eq**). From **2a-eq**, a dyotropic rearrangement involves the experimentally observed 1,2-shift of both the alkenyl and bromo groups to form **3a**. The barrier for this transformation is only 25.2 kcal/mol (Figure 3), and the reaction is exergonic by 5.0 kcal/mol.

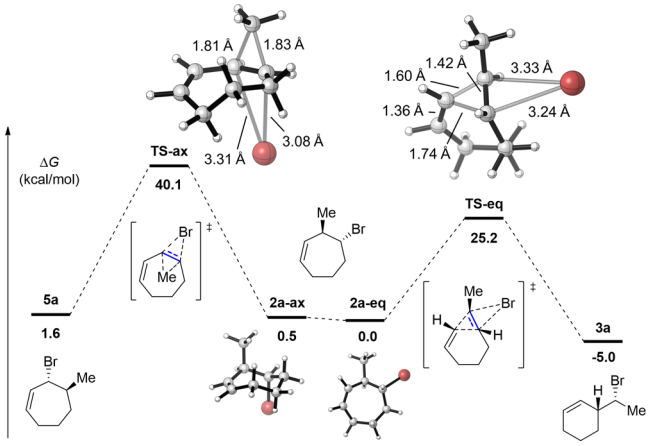

Figure 3. Calculated free energy profile for the concerted dyotropic rearrangements from the pseudoaxial (left part) or pseudoequatorial (right part) conformations of **2a**.

In contrast, the dyotropic rearrangement of the methyl and bromo groups from **2a-ax**, forming **5a**, has a significantly higher barrier of 40.1 kcal/mol. The calculated $\Delta G^{\ddagger}$ for **TS-eq** is consistent with our observations of a slow uncatalyzed transformation of **2a**–**e** to **3a**–**e** at room temperature in chloroform ($t_{1/2} \approx 6$ days).

Both **TS-eq** and **TS-ax** are highly polarized, with two long C–Br bonds (>3.0 Å) and two short C–C bonds, and as such can be described as tight ion-pairs of a carbocation and bromide anion. Indeed, the bromine atom in these two TSs bears an almost full negative charge (−0.95 to −0.97 au, see SI). This is in stark contrast to classical type I dyotropic rearrangements of vicinal dibromides, where the C–Br bonds were calculated to be around 2.5–2.8 Å.[8f] It is known that delocalization of the formed π bond in the TSs of dyotropic rearrangements provides key stabilization.[8d,e] In the case of **TS-eq**, the large polarization causes the carbon backbone of the substrate to approach the geometry of a $\pi\sigma$-delocalized bisected cyclopropylcarbinyl (nonclassical) cation (vide infra).[26,27] This greatly stabilizes the π bond of the TS (in blue, Figure 3) and explains why **TS-eq** has such a low barrier compared to **TS-ax**, for which the carbon backbone has the geometry of a less-stabilized corner-protonated cyclopropane.[28]

Having established that the enantiospecific uncatalyzed reaction is very likely to operate through a concerted dyotropic rearrangement, we investigated the role of an external Lewis acid (Figure 4). Formation of **2a·ZnBr$_2$** from the isolated reactants is favorable by 8.9 kcal/mol [see SI]. From this coordinated species, no concerted dyotropic transition states could be located; instead a stepwise mechanism is found.

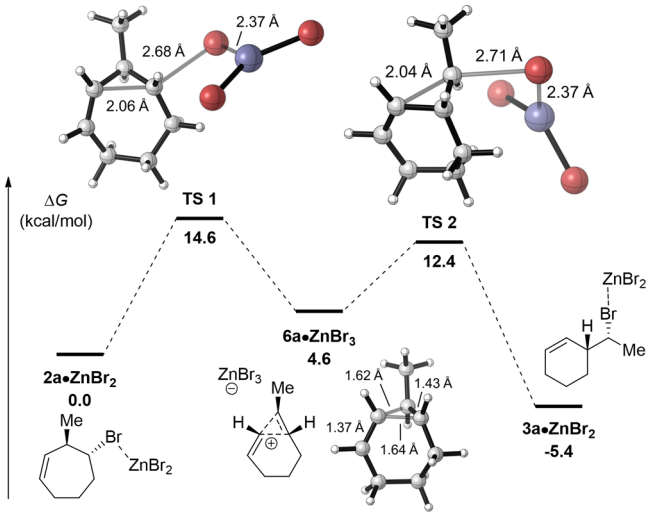

Figure 4. Calculated free energy profile for the stepwise transformation of **2a** to **3a**, catalyzed by $ZnBr_2$. For the structure of **6a·ZnBr$_3$**, the $ZnBr_3^-$ is hidden for clarity.

Ionization of the C–Br bond of complex **2a·ZnBr$_2$** through **TS 1** has a low barrier of 14.6 kcal/mol and leads to a contact ion-pair consisting of nonclassical cyclopropylcarbinyl cation **6a** and $ZnBr_3^-$. From this intermediate, only 7.8 kcal/mol is required to reach **TS 2**, where the C–Br bond of **3a** is formed. These calculations are consistent with the much faster reaction observed when $ZnBr_2$ is used as Lewis acid, since the activation barrier is predicted to be almost 10 kcal/mol lower than in the uncatalyzed case (14.6 vs 25.2 kcal/mol). While some stepwise ionic dyotropic rearrangements are known, these were limited to intramolecular examples (e.g., dyotropic rearrangement of Himbert cycloadducts via a zwitterion).[29,30] The present mechanism is an unprecedented case of a stepwise formal dyotropic rearrangement proceeding through an ion-pair.

Ionization of the C–Br bond in **TS 1** happens with simultaneous backside attack of the alkenyl group, analogous to an S_N2 mechanism. Similarly, bromide attack in **TS 2** occurs with release of the alkenyl group; therefore the C–Br bonds are broken and formed from the same face of **6a**, the structure of which is determined by the stereochemistry of **2a**. Thus **6a** is a *chiral* carbocation; however, even in the presence of Lewis acids such as $ZnBr_2$, the reaction of **2d** to **3d** was shown to be perfectly enantiospecific. We performed additional calculations to investigate the possible mechanism of racemization of **6a**. It is now well established that cyclopropylcarbinyl cations[26,27] are in equilibrium with the related bicyclobutonium cations, with the latter being more stable for the parent $C_4H_7^+$.[31,32] For the bicyclic cyclopropylcarbinyl cation **6a**, the profile is much more complex. The lowest-energy path for the racemization of **6a** is through the *meso*-bicyclobutonium **7a**, which is a TS (instead of a minimum) on the potential energy surface of cation **6a** (Figure 5).[33]

Once *chiral* cation **6a** is formed from the C–Br bond cleavage of **2a**, it requires an additional 10.9 kcal/mol of free energy to racemize through **7a·ZnBr$_3$**, a bicyclobutonium ion-pair. In contrast, it only needs 7.8 kcal/mol to recombine with the $ZnBr_3^-$ counteranion to form the stable product **3a** through **TS 2**. Moreover, the latter reaction is not reversible, as **3a·ZnBr$_2$** is 5.4 kcal/mol more stable than the starting complex. As such, there is a kinetic barrier to racemization in this system, allowing a stepwise enantiospecific rearrangement to occur.

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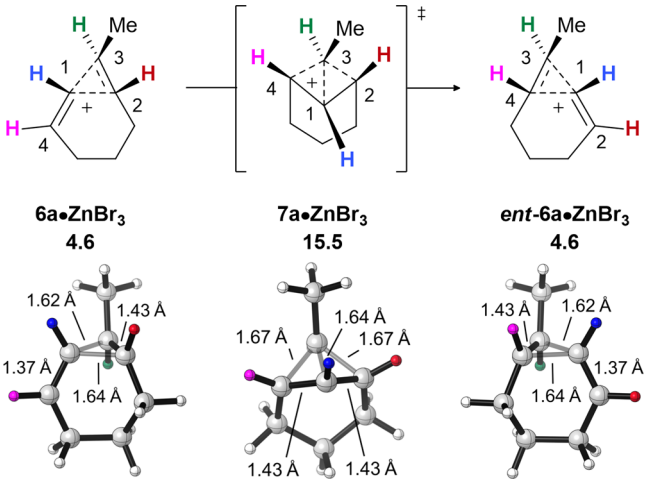

Figure 5. Lowest-energy pathway for racemization of **6a·ZnBr$_3$**. Free energies (kcal/mol) are relative to **2a·ZnBr$_2$** (Figure 4). The $ZnBr_3^-$ anions are hidden for clarity.

In summary, we have discovered an unanticipated ring contraction of bromocycloheptenes under mild conditions with remarkable regio- and stereochemistry. The ring contraction occurs via a double 1,2-migration of an alkene group and a bromide. DFT calculations show that the reaction proceeds through a nonclassical carbocation−anion pair; the $\pi\sigma$-delocalized bisected cyclopropylcarbinyl cation is crucial for the low activation barrier and enantiospecificity of the rearrangement. The reaction is concerted when uncatalyzed, presenting a rare type I dyotropic rearrangement of an alkene on a C−C stationary scaffold. In contrast, the reaction follows a stepwise mechanism under Lewis acid catalysis, and can be described as a formal dyotropic rearrangement. Our study also highlights how cations derived from chiral homoallylic halides may be productive intermediates in other enantiospecific reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b00821.

Experimental procedures and characterization data, and data for computed structures (PDF)
NMR and chiral GC spectra (PDF)
X-ray crystallographic data for compound **3d** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*houk@chem.ucla.edu
*b.l.feringa@rug.nl

ORCID

Pier Alexandre Champagne: 0000-0002-0546-7537
Makoto Fujita: 0000-0001-6105-7340
K. N. Houk: 0000-0002-8387-5261
Ben L. Feringa: 0000-0003-0588-8435

Present Address

‖S.S.G.: Institute of Materials Research and Engineering, 2 Fusionopolis Way, Innovis #08-03, Singapore 138634

Author Contributions

#S.S.G. and P.A.C. contributed equally.

Notes

The authors declare no competing financial interest.

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